REMARKS

Claims 1-33 and 43-51 were pending in this application prior to the Amendment presented above, and claims 1-15 were subject to examination in the outstanding Office Action dated October 23, 2008. Claims 1, 3, 4 and 9-12 have been amended as well as withdrawn claims 16, 19, 20 22, 27, 28, 32, 43 and 50. Claims 23-26 and 34-42 have been canceled as directed to non-elected inventions and to reduce excess claim fees without disclaimer of any subject matter or prejudice to the filing of a divisional application directed thereto. New claims 52-71 have been added.

New claims 52-57, 61, 66 and 71 are all dependent claims and recite that "the sample is from a subject with lupus." This claim language is supported throughout the application as originally filed and by original claim 2.

New independent claim 58 is similar to claim 1, but specifically recites in subparagraph (a): "a phospholipid that is soluble in the sample to a final concentration of 50 μM to 2 mM phospholipid." This language is supported by the specification as originally filed at page 14, lines 28-32.

New independent claim 62 recites in subparagraph (a): "a phospholipid that is soluble in the sample and contains no detectable aggregates as determined by quasi-electric light scattering techniques." This language is supported by the specification as originally filed at page 13, line 30 to page 14, line 2.

New independent claim 67 recites in subparagraph (a): "a phospholipid that is soluble in the sample and consists essentially of phospholipids acylated by C2 to C14 fatty acids." This language is supported by the specification as originally filed at page 14, lines 13-14.

New dependent claims 59, 64 and 69 recite that the "phospholipid is added to a final concentration of 200 μM to 2 mM." This language is supported by the specification at page 14, lines 28-32.

New dependent claims 60 and 65 recite "wherein the phospholipid comprises phospholipids acylated by C4 to C12 fatty acids." This claim language is supported by the application as originally filed at page 14, lines 13-14.

New dependent claims 63 and 68 particularly recite that the "phospholipid is added to a final concentration of 50 μM to 2 mM." This language is supported by the specification at page 14, lines 28-32.

New dependent claim 70 specifically recites that the "phospholipid consists essentially of phospholipids acylated by C4 to C10 fatty acids." This language is supported by the specification as originally filed at page 14, lines 13-14.

In view of the foregoing, it is respectfully submitted that the new claims present no new matter, and their entry and examination are respectfully requested.

Claim Objections.

The Office Action states that in claim 1, subparagraph (b), the term "thrombin activation" should be "prothrombin activation." The Applicants appreciate the Examiner's careful reading of the claims, and have amended "thrombin activation" to read as "prothrombin activation" in claim 1 as well as in withdrawn claim 27.

In addition, in claim 10, the Office Action states that the term "C6 phosphatidylserine" should be replaced by "1,2-dicaproyl-sn-glycero-3-phospho-L-serine (C6PS)." Claim 10 has been amended to recite "wherein the phospholipid consists essentially of phosphatidylserine acylated by C2 to C14 fatty acids," thereby mooting this objection.

Having addressed the objections to claims 1 and 10, it is respectfully requested that these objections be withdrawn.

35 U.S.C. §101.

Claims 1-9 and 10-14 stand rejected under 35 U.S.C. §101 as allegedly directed to non-statutory subject matter. In particular, the Office Action states that the recited method steps and compositions do not distinguish the claimed subject matter from naturally occurring methods and compositions (*e.g.*, the extrinsic/intrinsic clotting cascade). This rejection is addressed below.

The Applicants respectfully disagree with this rejection. For example, claim 1 is directed to a "method of evaluating clotting activity," which would indicate an assay method and, further, the claim language clearly indicates that the assay is performed on a "sample," which language would exclude the naturally occurring

intrinsic/extrinsic clotting cascades in an animal subject. Nonetheless, to advance the prosecution of this application, claim 1, subparagraph (a) has been amended to recite "combining *in vitro* a blood or plasma sample from a subject." Further, the preamble of claim 1 has been amended to recite a "method of evaluating clotting activity in a sample." Similar amendments have been made to claims 16, 22, 27, 28, 32, 43 and 50. Applicants note for the record that these amendments are merely clarifying the claimed subject matter and are not narrowing in effect.

Thus, claim 1 clearly and unambiguously recites an *in vitro* assay method and excludes the naturally occurring clotting cascades that occur *in vivo* in a subject, thereby overcoming this rejection and Applicants respectfully request its withdrawal.

35 U.S.C. § 112, second paragraph.

Claims 1-15 stand rejected under 35 U.S.C. §112, second paragraph as allegedly incomplete for omitting essential steps. The Office Action states that claim 1 is lacking a correlation step because the language of subparagraph (c) "detecting thrombin activity . . . indicative of clotting factor activity" allegedly does not correlate the detection with an evaluation of clotting activity. Claim 1, subparagraph (c) has been amended to recite "wherein the activity of Factor X_a or thrombin correlates with~~is indicative of~~ clotting factor activity in the sample, thereby evaluating clotting activity in the sample." Similar amendments have been made to claims 16, 22, 27, 28, 32 and 50. These amendments merely clarify the claimed subject matter and are not narrowing in effect.

Applicants respectfully submit that claims 1-15 satisfy the requirements of 35 U.S.C. §112, second paragraph and respectfully request that the rejection on this basis be withdrawn.

35 U.S.C. § 112, first paragraph (enablement).

Claims 1-14 stand rejected under 35 U.S.C. §112, first paragraph as allegedly not enabled. Specifically, the Office Action alleges that while the specification is enabling for contact activators selected from the group consisting of kaolin, clay, silica, CELITE, diatomaceous earth, glass beads, ellagic acid, or a combination

thereof, it does not provide enablement for the genus of "contact activators" as recited by claim 1. The Office Action further argues on page 6 (¶ 1) that the "Applicant fails to set forth the criteria that define a 'contact activator' other than providing a functional definition of 'contact activator' as 'particular and chemical contact activators'." The Office Action further asserts:

> Attention is directed to *General Electric Company v. Wabash Appliance Corporation* 37 USPQ 466 (US 1938), at 469, speaking to functional language at the point of novelty as herein employed: "the vice of a functional claim exists not only when a claim is 'wholly' function, if that is ever true, but when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty'. Functional language at the point of novelty is further admonished in *University of California v. Eli Lilly and co.* 43 USPQ2nd 1398 (CAFC 1997) at 1406: stating this usage does 'little more than outline goals appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate'.

Office Action, page 6, ¶ 1 (*emphasis added*).

Applicants respectfully note that the use of a contact activator in the claimed methods or kits can in no way be construed as the "point of novelty" of the present invention. Contact activators are conventional, commonplace and well-known in the art. Further, although contact activators are employed in the claimed methods, it would be readily apparent to the skilled worker that such contact activators do not represent the inventors' contribution to the art and are certainly not relied upon for the novelty of the claimed methods or kits. Accordingly, the citations to *General Electric Company v. Wabash Appliance corporation* and *University of California v. Eli Lilly and Co.* are inapposite.

The present inventors' have discovered that phospholipids that are soluble in blood or plasma samples can be used in place of conventional insoluble phospholipids (*e.g.*, isolated phospholipids from naturally occurring sources or synthetic membrane preparations) in clotting assays and assays to evaluate clotting factor activity. The soluble phospholipids of the invention can be employed in any such assays, numerous of which are known in the art. The use of soluble phospholipids has a number of advantages over prior art reagents (*e.g.*, membrane

preparations from natural sources or synthetic preparations) including improved reproducibility, ease of manufacture, and improved shelf life, and may additionally be better suited for use in assays with blood or plasma samples from Lupus patients (*see, e.g.,* specification at page 4, lines 9-12).

The choice of contact activator to use in the recited methods and kits would be routine to the skilled worker using the knowledge and techniques readily available in the art. For example, U.S. Patent No. 4,455,377 (issued in 1984) discloses colloidal silica and colloidal alumina-coated silica as a contact activator. As another illustration, U.S. Patent No. 5,443,960 ("the '960 patent"; issued in 1995) describes contact activators including kaolin, celite and ellagic acid (col. 3 lines 30-32). Moreover, claim 22 of the '960 patent, which is entitled to a presumption of validity, generically recites "contact activator" without further recitation of any specific contact activators. Another exemplary patent is U.S. Patent No. 6,221,672 ("the '672 patent"; issued in 2001), the specification of which describes contact activators as including kaolin, diatomaceous earth, powdered glass, silica or any other particle having a negative charge (col. 6, lines 3-12). Claim 1 of the '672 patent, which is presumed to be valid, also generically recites a "contact activator." Copies of U.S. Patent Nos. 4,455,377; 5,443,960; and 6,221,672 are enclosed for the Examiner's convenience. These patents demonstrate that the term "contact activator" is well-understood in the art, that various contact activators have long been known in the art, and further that the generic recitation of the term "contact activator" is found in the claims of issued U.S. patents.

Accordingly, the present specification need not disclose the physical characteristics of the numerous possible contact activators in order to enable the claimed invention. A specification need not supply information that is well-known in the art in order to satisfy the enablement requirement, and preferably omits such information. *See Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997); *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."); *see also* MPEP 2164.01.

In view of the foregoing discussion and the cited U.S. patents and case law, the Applicants respectfully submit that the specification enables the practice of the claimed methods and request that the outstanding rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

35 U.S.C. § 102(b).

The claims are subject to two rejections on the basis of lack of novelty under 35 U.S.C. § 102(b), each of which will be addressed individually below.

1. Gempeler et al.

Claims 1, 3, 5-10, 13 and 14 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by International Patent Publication WO 01/44493 (Gempeler et al.) as evidenced by Hürter. The Office Action states:

> Gempeler anticipates the claims by teaching a body fluid coagulation-potential assay comprising a body fluid, including plasma; contacting with phospholipids, calcium ($CaCl_2$), and an activator (e.g. RVV-V).... To the extent that Gempeler may be silent with respect to the presence/degree thereof of a particular phospholipid, as evidenced by Hürter, plasma intrinsically comprises a degree of phospholipids, including phosphatidylserine (PS) and phosphatidylethanolamine (PE) among others) (Hürter, table II).

(Office Action, ¶ spanning pages 7-8; *emphasis added*).

To anticipate a claim, each and every element of the claim must be taught, either expressly or inherently, in a single prior art reference. *See e.g., Verdegaal Bros. v. union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) ("a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference"). The outstanding rejection fails to satisfy the legal requirements for anticipation as each and every element of the claimed invention is not disclosed by the Gempeler et al. reference. At a minimum, Gempeler et al. fails to disclose a "phospholipid that is soluble in the blood or plasma sample" as recited by claim 1, and the outstanding rejection is silent on this feature of the claims. As such, the rejection over Gempeler et al. is legally deficient and cannot be maintained.

As described in the present specification at page 13 (lines 27-28), a soluble phospholipid "comprises essentially no aggregates (*e.g.*, as lamellar or non-lamellar structures)." In contrast, Gempeler et al. only discloses use of conventional, insoluble (*i.e.*, aggregated, solid-phase) phospholipids that are prepared from natural sources.

Most of the Gempeler et al. application simply refers to "phospholipids" (*see, e.g.*, the abstract; page 4, line 18; page 6, lines 7 and 16; and page 8, line 13). This generic reference to "phospholipids" fails to disclose or suggest the claimed methods employing "phospholipids that are soluble in the blood or plasma sample" to the worker ordinarily skilled in the art. At page 10, lines 14-15, Gempeler et al. states that "the activator reagent includes a predetermined amount of natural or synthetic phospholipids or platelets." Platelets and "natural" phospholipids are clearly insoluble; as discussed in more detail below, all naturally occurring phospholipids will spontaneously form membrane-like structures or other aggregated phases at the concentrations required for a clotting assay. Likewise, one ordinarily skilled in the art would have understood the reference to "synthetic phospholipids" to mean insoluble synthetic membranes, which are conventional in the art (*see, e.g.*, specification at page 13, lines 4-9).

It is well-established in the art that phospholipids isolated from natural products such as animal, plant or microbial sources are insoluble[1]. In particular, these phospholipids from natural products have fatty acids with hydrocarbon chains that are generally C16 or longer[2], and which spontaneously form aggregates or other membrane-like structures[3]. This property is not surprising as the source of

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[1] *See, e.g.*, Bloor, W.R., Biochemistry of the Fats. *Chem. Rev.* 2: 243-300 (1925) (*copy enclosed*).

[2] *See, e.g.*, Tables 28-4 and 28-5 from Marcus, A.J., Chapter 28 "Multicellular Eicosanoid and Other Metabolic Interactions of Platelets and Other Cells" *in* Hemostasis and Thrombosis: Basic Principles and Clinical Practice, Vol 3, 1994, JB Lippincott, Philadelphia, PA (*copy enclosed*). *See also*, page 97 of Tanford, C., Chapter 12 "Biological Lipids" *in* The Hydrophobic Effect: Formation of Micelles and Biological Membranes, 1973, John Wiley & Sons, New York, NY (*copy enclosed*).

[3] *See, e.g.,* Tanford, C., Chapter 12 "Biological Lipids" *in* The Hydrophobic Effect: Formation of Micelles and Biological Membranes, 1973, John Wiley & Sons, New York, NY (*copy enclosed*), for example, the discussion at page 98 (second para) and at pages 99-100 ("Critical Micelle Concentration") (*copy enclosed)*.

phospholipids in natural products is primarily from cellular membranes. Phospholipid preparations isolated from natural sources are commonly referred to as "synthetic membranes." Synthetic membrane preparations are conventional in the art and are discussed in the present specification at page 13, lines 4-9 and 15-18[4].

Further, any reference in Gempeler et al. to a particular phospholipid source is exclusively to insoluble phospholipid preparations. For example, at page 12, lines 10 and 25, Gempeler et al. describes activator reagents comprising 25 or 50 μg/ml phospholipids, respectively, from rabbit brain cephalin, which is a standard source of natural phospholipids in the prior art and will spontaneously form insoluble membrane structures in aqueous solution such as a blood or plasma sample (*see also*, Gempeler et al., page 16, line 15).

In contrast, the present invention uses phospholipid preparations that are soluble in blood or plasma samples. As far as the inventors are aware, there is no description in the prior art of phospholipid reagents that are soluble in blood or plasma samples for use in clotting assays or methods of performing clotting assays using such a soluble phospholipid preparation. As described in the application:

> The finding that a solubilized phospholipid can replace a phospholipid-containing membrane in the intrinsic clotting cascade and is functionally equivalent thereto is quite surprising. The current understanding of the intrinsic pathway is that a two-dimensional membrane surface is required to bring the individual factors together and to accelerate complex formation. The present inventors have discovered that, in fact, the membrane surface itself is dispensible; phospholipid molecules, whether membrane-bound or in a solubilized form, have specific regulatory and second messenger activity that result in acceleration of the clotting cascade.

(Specification page 11 line 31 to page 12 line 6; *emphasis added*).

Turning to Hürter et al., Applicants are unclear about the reliance on this reference in the outstanding rejection. The Office Action states that Hürter et al. teaches that plasma inherently contains phospholipids including phosphatidylserine (PS) and phosphatidylethanolamine (PE). However, the presence of PS and PE in plasma is not relevant to the present invention or to the phospholipids used in the

[4] *See also,* Okuda et al. Usefulness of synthetic phospholipid in measurement of activated partial thromboplastin time: a new preparation procedure to reduce batch difference. *Clin. Lab. Haematol.* 26: 215-223 (2004) (*copy enclosed).*

"activator reagent" disclosed by Gempeler et al. Further, the presence of PS and PE in plasma does not address the issue of whether Gempeler et al. discloses phospholipid preparations that are soluble in blood or plasma samples; PS and PE can exist in insoluble phospholipids. In the context of a clotting assay, it is the length of the hydrocarbon tail of the fatty acid moieties in the phospholipid that primarily determines solubility of the phospholipid in aqueous solutions such as blood or plasma samples. The effect of the head group (*e.g.*, PS or PE) is minimal in determining solubility. As discussed in more detail above, naturally occurring sources of phospholipids will primarily have fatty acids with hydrocarbon tails that are C16 or longer and will form insoluble membrane structures in aqueous solutions. The inventors are not aware of soluble phospholipids naturally occurring in plasma or any other biological system. The existence of lipids in plasma does not suggest that they are soluble. In fact, it is well-known in the art that plasma contains lipoprotein particles such as high density lipoproteins (HDL), low density lipoproteins (LDL), chylomicrons, and the like, which incorporate phospholipids as micellar lipids.

In view of the foregoing discussion, it is clear that Gempeler et al. fails to disclose each and every element of the claimed invention. Accordingly, the Applicants respectfully request that the outstanding anticipation rejection over Gempeler et al. be withdrawn.

If the present rejection is maintained, it is respectfully requested that the Examiner specifically point out how Gempeler et al. allegedly discloses phospholipid preparations that are soluble in blood or plasma samples so that Applicants can more efficiently address the Examiner's concerns and expedite the prosecution of this application to allowance.

2. Triplett et al.

Claims 1, 2, 5, 7 and 8 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,705,198 (Triplett et al.) as evidenced by Hürter. The Office Action states that "Triplett teaches combining a plasma sample; soluble phospholipids, including phosphatidylserine and phosphatidylethanolamine obtainable by extraction or commercially available; a contact activator; and calcium

(chloride), including the incubation thereof to activate thrombin/detect thrombin activity (abstract; summary; column 5, ¶ 3, 4; examples 4 and 5)." Applicants have studied the cited sections in the Triplett et al. patent and can find no disclosure or even a suggestion of using phospholipids that are soluble in blood or plasma samples. The cited text at column 5, ¶ 3, 4 of Triplett et al. exclusively concerns insoluble phospholipids. Likewise, Examples 4 and 5 of Triplett et al. use the phospholipid preparation of Example 2 – from rabbit brain kephalin, which is a conventional, insoluble (*i.e.*, membrane) source of phospholipids.

Triplett et al. only discloses use of conventional, insoluble (*i.e.*, aggregated, solid-phase) phospholipids that are prepared from natural sources. For example, at page 4 (lines 23-25), Triplett et al. states that "[a] clotting test, sensitive to LA can be carried out by mixing a plasma sample with a suitable amount of a phospholipid suspension . . .." (*emphasis added*). Applicants respectfully note that a "suspension" is "a dispersion of fine solid particles in a liquid or gas, removable by filtration" (Encarta dictionary). Thus, the "phospholipid suspension" of Triplett et al. is composed of insoluble phospholipid particles.

> Further, at Col. 5 (lines 25-32), Triplett et al. teaches that:
>
> Phospholipids suitable for the performance of the PLDPA tests are preparations containing phosphatidylethanolamine (Synonym: colamine kephalin) and phosphatidylserine (Synonym: serine kephalin) which are obtainable from animal, plant or microbial biomass by organic solvent extraction. Suitable phospholipid preparations e.g. from bovine brain, egg yolk or soy bean are commercially available from Sigma Chemical Company, St. Louis, Mo., USA.

Likewise, the Examples of the Triplett et al. patent use phospholipids prepared from rabbit brain. As discussed at some length in the preceding section in connection with the rejection over Gempeler et al., essentially all of the phospholipids isolated from natural products such as animal, plant or microbial sources have fatty acids that are C16 or longer and spontaneously form micelles or other membrane-like structures in aqueous solutions such as blood or plasma samples. Thus, the phospholipids taught by Triplett et al. are all conventional, insoluble preparations isolated from natural sources.

In sum, the present invention is novel over Triplett et al., which fails to disclose methods of evaluating clotting activity in a sample using a phospholipid reagent that is soluble in a blood or plasma sample. Accordingly, Applicants respectfully request that the rejection under §102 (b) on this basis be withdrawn.

Again, if the present rejection is maintained, it is respectfully requested that the Examiner specifically point out how Triplett et al. allegedly discloses soluble phospholipid preparations that are soluble in blood or plasma samples so that Applicants can more efficiently address the Examiner's concerns and expedite the prosecution of this application to allowance.

35 U.S.C. § 103(a).

The Office Action also raises two rejections under 35 U.S.C. §103(a).

1. Gempeler et al. or Triplett et al., the Sigma catalog, and Matschiner et al. in view of Hürter.

Claims 1-15 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable for obviousness over Gempeler et al. or Triplett et al. and pages 782-791 of the Sigma catalog and U.S. Patent No. 5,525,478 (Matschiner et al.) in light of Hürter. The Gempeler et al., Triplett et al. and Hürter references are discussed above. The Sigma catalog is cited for the teaching of dried PE and PS, and Matschiner et al. is cited for the teaching of protein S depleted plasma. The Sigma catalog and Matschiner et al. do not disclose or suggest a phospholipid reagent that is soluble in blood or plasma samples or assays using the same and therefore fail to remedy the deficiencies of Gempeler et al., Triplett et al. and Hürter. The Applicants therefore respectfully submit that the subject matter of claims 1-15 is nonobvious over the combination of Gempeler et al. or Triplett et al., the Sigma catalog, and Matschiner et al. in view of Hürter.

2. Tans et al.

Claims 1, 3-5, 7 and 9-15 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable for obviousness over Tans et al., *J. Biol. Chem.* 266:21864-21873

(1991). The Office Action states that "Tans also teaches contacting a prothrombin sample with a 10μM PS-containing phospholipid (50μM total phospholipid), calcium ($CaCl_2$), and a contact activator (e.g., *E. carnitus* venom); incubation at 37°C; and quantitative analysis of thrombin (assay 1)(e.g. Methods, ¶1 (proteins) and 8 (quantitative analysis) pages 21865-28666)." This rejection is addressed below.

Applicants respectfully submit that Tans et al. fails to disclose or suggest the use of a phospholipid that is soluble in a blood or plasma sample as recited by the present claims. For at least this reason, Tans et al. fails to render the claimed subject matter obvious.

Turning to the sections specifically relied upon in formulating the outstanding rejection, paragraph 1 (Proteins) of the "Methods" section explicitly states that "phospholipid vesicles" are used. Phospholipid vesicles are small (10 – 10,000 nm) particles in which a lipid lamellar phase encloses a trapped volume, and are by definition insoluble structures[5]. Paragraph 8 (Quantitative Analysis of Prothrombin Activation"), lines 1-3, states that "[r]ates of prothrombin activation in the purified system were determined under initial rate conditions as described earlier," citing Rosing et al., *J. Biol. Chem.* 255:274-283 (1980) (copy enclosed). Further, ¶4 (Lipid Preparations) states: "Phospholipid vesicles were prepared as described earlier," again citing Rosing et al. Thus, Tans et al. again explicitly states that the phospholipid preparations used in the prothrombin activation assay were phospholipid vesicles. Moreover, Rosing et al. describes "Phospholipids and Phospholipid Vesicle Preparations" at page 275, right col. ¶1. At the end of this paragraph, Rosing et al. expressly states that "[t]he vesicle preparations described above were used throughout our experiments and were chosen because they exhibit excellent clot-promoting activity." (*emphasis added*). Thus, Tans et al. (and Rosing et al.) exclusively describe the use of insoluble phospholipid preparations and fail to disclose or suggest the use of a phospholipid that is soluble in a blood or plasma sample as recited by the present claims.

[5] *see, e.g.*, Thompson et al., A Calorimetric and Fluorescent Probe Study of Phase Transitions in Phosphatidylcholine Liposomes. In "Biochemistry of Membrane Transport" [ed] G. Semenza and E. Carafoli, Springer-Verlag, Heidelberg, 47-71, 1977 (*copy enclosed*).

Accordingly, in light of the foregoing discussion, Applicants respectfully submit that the subject matter of claims 1, 3-5, 7 and 9-15 is nonobvious over Tans et al. and respectfully request that the rejection under 35 U.S.C. §103(a) over this reference be withdrawn.

New Claims.

New claims 52-71 are enabled and free of the cited art for the reasons addressed above with respect to claims 1-15.

In addition, new independent claim 58 specifically recites in subparagraph (a): "a phospholipid that is soluble in the sample to a final concentration of 50 μM to 2 mM phospholipid." As addressed at length above, the cited references fail to disclose or suggest the use of a soluble phospholipid. More specifically, with respect to independent claim 58, these references fail to disclose a "a phospholipid that is soluble in the sample to a final concentration of 50 μM to 2 mM phospholipid." As discussed in more detail above, the conventional, art-known phospholipids used in clotting assays and assays to evaluate clotting factor activity would all form insoluble membrane-like structures at the recited concentrations.

New independent claim 62 recites in subparagraph (a): "a phospholipid that is soluble in the sample and contains no detectable aggregates as determined by quasi-electric light scattering techniques." The cited references do not disclose or suggest using a soluble phospholipid reagent that comprises "no detectable aggregates as determined by quasi-electric light scattering techniques" or any other technique. As discussed above, there is no suggestion of using soluble phospholipids at all.

New independent claim 67 recites in subparagraph (a): "a phospholipid that is soluble in the sample and consists essentially of phospholipids acylated by C2 to C14 fatty acids." None of the cited references, individually or in any combination, disclose or suggest a phospholipid that consists essentially of phospholipids acylated by C2 to C14 fatty acids. Indeed, there is no suggestion whatsoever of using C2 to C14 fatty acids, which are not present in naturally occurring phospholipids or are present at negligible quantities[2].

Therefore, Applicants respectfully submit that the subject matter of claims 52-71 is enabled and patentable over the cited references.

Conclusion.

The points and concerns raised by the Examiner in the outstanding Office Action having been addressed in full, it is therefore respectfully asserted that this application is in condition for allowance, which action is respectfully requested. Should the Examiner have any remaining concerns, it is respectfully requested that he contact the undersigned attorney at (919)-854-1400 to expedite the prosecution of this application to allowance.

Respectfully submitted,

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Enclosures:
- Thompson et al.
- Bloor et al.
- Marcus et al.
- Tanford et al.
- Okuda et al.
- Rosing et al.
- U.S. 4,455,377
- U.S. 5,443,960
- U.S. 6,221,672

CERTIFICATION OF TRANSMISSION

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